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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SMITH, LYNETTE F	

ART UNIT	PAPER NUMBER
1645	11

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary

Application No.	Applicant(s)
09/555,139	Aglsteribbe, et al
Examiner	**Art Unit**
Lynett R. F. Smith	1645

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on 3/25/02

2a) [ ] This action is **FINAL.** 2b) [X] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) 10-23 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) 10-23 is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirem

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [X] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [X] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____.
3. [X] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [X] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The examiner acknowledges the preliminary amendment filed 3/24/00. Claims 1-9 have been canceled and new claims 10-23 have been added. Therefore, claims 10-23 are pending and under consideration.

3. The use of the trademark EPISERF has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. In view of applicant's preliminary amendment and cancellation of claims 1-9, all previous rejections of record are withdrawn.

NEW GROUNDS OF REJECTION

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 10-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine comprising LTB ans influenza hemagglutinin, as well as methods of inducing an immunoglobulin response against influenza HA and methods of preparing LTB and influenza HA, does not reasonably provide enablement for any vaccine comprising any immunogen, methods of preparing any vaccine and methods of inducing a mucosal response against any immunogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are broadly drawn to vaccine compositions comprising any particulate immunogen combined with LTB, methods of inducing an mucosal response against any immunogen as well as methods of preparing any immunogen. The claims encompass a myriad of immunogens which includes vaccines against HIV. The specification does not enable the broad scope of the claimed invention.

The specification provides no probative evidence to support the claimed enablement of a vaccine which would protect humans against AIDS, for example. There is no evidence that the claimed vaccine preparation was ever given to humans. The obstacles to vaccine development and therapeutic approaches with regard to retroviruses associated with AIDS in humans are well documented in the literature. These obstacles include: 1) the extensive genomic diversity associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form, as well as via free virus

transmission, 3) existence of a latent form of the virus, 4) the ability of the retrovirus to "hide" in the central nervous system where blood cells and neutralizing agents carried by the blood cannot reach the retrovirus, due to the blood-brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establish that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any vaccine or any immunization treatment or any therapeutic regimen on its face (See for example Fox, 1994, Bio/Technology, Volume 12, page 128 "No Winners Against AIDS", in which it is stated that "No therapy has emerged as a sure winner in the campaign against HIV...", copy enclosed). In order to provide proof of enablement with regard to vaccines and their uses, either clinical or in vivo or in vitro data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See In re Irons, 340 F.2d 924, 144 USPQ 351 (CCPA 1965), Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat. App. & Inter. 1986) and Ex parte Chwang, 231 USPQ 751 (PTO Bd. Pat. App. & Inter. 1986). When the utility is directed to humans the data must generally be clinical, however, adequate animal data would be acceptable in those instances wherein one of ordinary skill in the art would accept the correlation to human utility. Thus in order to rely on animal data there must exist an art-recognized animal model for testing purposes. See In re Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962). With respect to the AIDS-associated retroviruses the art does not recognize any animal model as exhibiting a direct correlation to human disease. To date the chimpanzee is the best available animal model for the study of AIDS in humans because it is the

only one capable of infection with the HIV or HTLV III/LAV virus. The chimpanzee however, does not develop the full blown syndrome of AIDS, the significance of this failure being the inability to assess challenge after treatment with the purported vaccine (see for example, Feinberg et al, "AIDS vaccine models: Challenging challenge viruses", 2002, Nature Medicine 8(3):207-210, and Haynes, et al, 1996, "Update on the issues of HIV vaccine development", Ann. Med. 28:39-41, copies enclosed). By definition vaccines must not only induce an immune response, but must be immunogenic to the extent that upon subsequent challenge with the live virus, development of the disease is prevented, or better yet infectivity does not occur. In view of all of the above and in view of the state of the art, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claimed subject matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of the claims is not as precise as the subject matter permits such that one may reasonably know the metes and bounds of the claims. The claims are indefinite in the recitation of "characteristics of E. coli" because it is unclear from the specification what

applicant intends. The claims are also indefinite because it is unclear from the specification what applicant intends by the recitations "disease which is transmitted by mucosal infection", "characteristic of a micro-organism", "common mucosal immune response" and "sufficient quantity". Claims 12 and 23 are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y). Clarification and correction are required in order to obviate this rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 10-16, 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamura et al, U.S. Pat. No. 5,182,109. The claims are broadly drawn to a vaccine comprising at least one particulate immunogen combined with B subunits of heat-labile enterotoxin characteristic of E. Coli and free from A subunits and toxic LT holotoxin. It should be noted that the examiner is viewing the recitations of "particulate" and "recombinant DNA methods" as process limitations.

Tamura et al teach a vaccine composition comprising the LTB heat-labile toxin B subunit from E. Coli and influenza hemagglutinin (HA) antigens (abstract, column 3 and claims 1-7). The vaccine of Tamura et al is the same as the claimed vaccine. Limitations such as "free from A subunit and toxic LT holotoxin", "characteristic of E. Coli" and "characteristic of a micro-organism" would be inherent in the vaccine composition of Tamura et al. Additionally, as previously stated, limitation such as "particulate" and "recombinant DNA methods" are being viewed as process limitations. The products of the prior art reference appear to be the same as the product claimed by applicant because they appear to possess the same or similar functional characteristics, i.e (). The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when the properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPQ 964 (CAFC 1985); In re Marosi, 218 USPQ 289, 29222-293 (CAFC 1983); In re Brown, 173 USPQ 685 (CCPA 1972). Even if applicant's product is of a higher purity than that of the prior art product, applicant's product would have been prima facie obvious over the product of the prior art since one of ordinary skill in the art, being motivated by the expectation of success and the attainment of greater specific activity with increased purity, could have used conventional techniques in the product art to further purify and characterize the product. Thus even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in

specific activity with the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the obviousness aspect of this rejection, i.e. assuming the aspect of the product's purity is relied upon. Moreover, since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i.e., that the composition of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

8. Claims 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Tamura et al, U.S. Pat. No. 5,182,109. The claims are drawn to a method of inducing a systemic immunoglobulin response against an immunogen comprising administering the particulate immunogen and LTB adjuvant.

Tamura et al teach a method of preparing a vaccine comprising combining one or more immunogens with heat-labile toxin subunit B from E. Coli or cholera toxin subunit B. Tamura et al teach administration of the vaccines to mice, mucosally to induce the production of immunoglobulin (columns 4-21). The methods of Tamura et al are the same as the claimed

methods. Limitations such as free from subunit A and LT holotoxin, "common mucosal immune response", "sufficient quantity" and induction of systemic immunoglobulin response would all be inherent in the methods of Tamura et al. Since the Office does not have the facilities for examining and comparing applicants' method with the method of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material structural and functional characteristics of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. Claims 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kikuta et al or Hirabayashi et al. The claims are drawn to a vaccine comprising the particulate immunogen and B subunits of cholera toxin or enterotoxin.

Kikuta et al (abstract, pages 595-596) or Hirabayashi et al (abstract and pages 243-244) teach vaccine compositions comprising influenza HA antigens and cholera toxin subunit B. The vaccine composition of either Kikuta et al or Hirabayashi et al is the same as the claimed vaccine composition. Characteristics such as free of A subunits and LT and CT holotoxin would be inherent in the vaccine composition of the prior art references. Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed composition and the composition of the prior art (i.e., that the composition of the prior art does

not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

10. Claims 10-18 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Nashar et al. The claims are drawn to vaccine compositions and methods of inducing systemic immunoglobulin responses.

Nashar et al teach vaccine compositions comprising an immunogen (antigen from *Streptococcus mutans*) and heat-labile subunit B toxin from E. Coli or the immunogen and cholera subunit B toxin (abstract, pages 235-239). Nashar et al also teach methods of inducing immunoglubulin responses as well as methods of preparing the vaccine compositions. The vaccine and methods of Nashar et al are the same as the claimed vaccine and methods. Limitations such as "particulate" and "recombinant" are being viewed as process limitations. Characteristics such as free from A subunits and LT holotoxin and mucosal immune responses would be inherent in the vaccine and method of Nashar et al.

11. Claims 10-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirst et al, WO 90/06366. The claims are drawn to vaccine compositions, methods of preparing the vaccine compositions and methods of inducing mucosal immune responses.

Hirst et al teach vaccine compositions comprising fusion proteins (immunogens which can comprise antigens from influenza viruses, Herpes Simplex Viruses and hepatitis viruses) and heat-labile subunit B toxin from E. Coli (LTB) (pages 2-8). The compositions were generated and used to immunize animals for the development of antibody responses (abstract and pages 2-8). The vaccine compositions and methods are the same as the claimed vaccine composition and methods.

12. Claims 10-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Fujisawa et al, U.S. Pat. No. 5,241,053. The claims are drawn to vaccine compositions, methods of preparing the vaccine compositions and methods of inducing mucosal immune responses.

Fujisawa et al teach fusion proteins compositions produced and expressed recombinantly, comprising the gene encoding LTB and glycoprotein D from herpes simplex virus. Fujisawa et al teach that the fusion proteins may be formulated int vaccine compositions and administered to animals (columns 1-6, 7-12, abstract and claims). The fusion protein compositions and methods of the prior art are the same as the claimed vaccine composition and methods. Since the Office does not have the facilities for examining and comparing applicants' composition and methods with the composition and method of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed composition and methods and the composition and methods of the prior art (i.e., that the composition and method of the prior art does not possess the same material structural and functional characteristics of the claimed composition and methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Tamura et al, (1992, Journal of Immunology, 149(3):981-988) teach vaccine compositions comprising cholera toxin subunit B and influenza antigens. Smerdou et al, (1996, Virus Research, 41:1-9) teach compositions comprising E. Coli heat-labile subunit toxin B and gastroenteritis virus S protein expressed n Salmonella.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SPE Lynette F. Smith whose telephone number is 703-308-3909. The examiner can normally be reached on Mondays - Thursdays from 7:30am to 5:00pm. The examiner can also be reached on alternate . The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Smith/lfs
June 26, 2002

L. F. Smith

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